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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/446,200	05/19/95	FREEMAN	G RPI-033

EXAMINER

18M1/0611

LAHIVE & COCKFIELD
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ART UNIT	PAPER NUMBER
1816	8

DATE MAILED: 06/11/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 3/13/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(e).

Disposition of Claims

☒ Claim(s) 1-59 is/are pending in the application.
Of the above, claim(s) 5-59 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-4 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. Substitute
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, Claims 1-11; the specific method of modulating, that of stimulating a Th2 response; and the specific agent, that of a stimulatory form of B7-2 attached to a solid support, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that Groups I-IV should be regrouped into a single group. This is not found persuasive because claims in Groups I-IV recite different methods of use. These inventions require different ingredients, process steps and endpoints to accomplish the use of stimulating with a second activation signal, cells which have already received the first activation signal; activating cells with the primary activation signal, and stimulating cells *ex vivo*.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-59 are pending in the application. Claims 2-4 are readable on the elected species. Claims 5-59 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as drawn to a non-elected invention. Claims 1-4 are currently under examination.

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed, see substitute PTO-948.

Claim Rejections - 35 USC § 112

4. Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 2 is indefinite for reciting "wherein the Th2-type response is stimulated" because it is not clear what is meant by stimulating an ongoing Th2-type response. If the meaning intended is that of skewing the response towards being a Th2 response or inducing a Th2 response, it is suggested that the claim be changed to recite "wherein a Th2 response is induced".

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the

examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hathcock *et al.* [J. Exp. Med. 180: 631-640 (Aug 1994)] in view of Linsley *et al.* [U.S. Patent 5,580,756 (102(e) Date: Mar 1990)], Kuchroo *et al.* [Cell 80: 707-718 (Mar 1995)] and Janeway *et al.* [Cell 76: 275-285 (Jan 1994)].

Hathcock *et al.* teach the expression, regulation and function of B7-2. Hathcock *et al.* teach that B7-1 and B7-2 are expressed/induced with differing kinetics and play different roles in initiating and maintaining an immune response. For example, Hathcock *et al.* teach that in response to LPS or anti-IgD-dextran, murine B cells express B7-2 earlier and at higher levels than B7-1 and that such quantitative differences in the amount of B7-1 and B7-2 expressed on activated B cells may profoundly influence their contribution to costimulatory function (Pages 634 and 638, in particular).

Hathcock *et al.* do not teach using immobilized B7-2 to stimulate activated T cells and induce their differentiation into Th2 cells. However, Linsley *et al.* teach using soluble B7 including fragments and derivatives to stimulate T cells. Linsley *et al.* teach that B7 antigen is reacted with T cells *in vitro* to crosslink or aggregate the CD28 receptor, for example, using CHO cells expressing B7 antigen or immobilizing B7 on a solid substrate, to produce activated T cells (Column 12, Lines 14-17, in particular). Linsley *et al.* teach that T cells are activated with anti-CD3 and the further stimulated with either a stimulating anti-CD28 antibody or soluble B7-Ig fusion protein. Immobilized soluble B7 enhances proliferation of activated T cells (Column 32 and Table 2, in particular).

Linsley *et al.* do not teach that activation of T cells using immobilized soluble B7-2 induces Th cells to differentiate to Th2 cells. However, Kuchroo *et al.* teach that their data in experiments using anti-B7-1 and anti-B7-2 antibodies are direct evidence that interaction of the costimulatory molecules B7-1 or B7-2 with their counterreceptors CD28 and CTLA-4 on T helper precursors (Thp) during antigen presentation leads to polarization of Th responses and that the simplest interpretation of their data is that B7-1 preferentially acts as a costimulator for the generation of Th1 cells while B7-2 costimulates and induces Th2 cells (Page 715, Column 1 and Figure 7, in particular). Kuchroo *et al.* teach that the identification of intracellular signals that are generated by interaction of B7-1 and B7-2 with the same counterreceptors (CD28 and CTLA-4) on a Thp cell may provide insight into the molecular mechanisms responsible for Th cell differentiation, allowing selective manipulation of the immune response in disease (Page 715, Last paragraph, in particular). Janeway *et al.* teach that one of the most crucial events in the differentiation of naive CD4 T cells that respond to ligand presented together with costimulators is the decision whether to become a helper CD4 T cell (Th2), specialized for the activation of B cells to secrete antibody, or an inflammatory CD4 T cell (Th1), specialized to activate macrophages and stimulate cell-mediated immunity (Page 281, Column 2, in particular). Janeway *et al.* teach that if the biochemical nature of differential signaling pathways are known, pharmacological agents can be developed capable of diverting T cell responses from harmful to innocuous by getting the T cell to reinterpret the signals it is receiving via its receptors.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to stimulate CD3-activated T cells to differentiate to Th2 cells by activating them with immobilized soluble B7-2. One would have been motivated to substitute soluble B7-2 for B7 in the teachings of Linsley *et al.* because of Hathcock's teaching of B7-2 on activated B cells, Kuchroo's teaching that interaction with B7-2

induces activated T cells to differentiate to become Th2 cells, and Linsley's teaching that immobilized soluble B7 is very effective. One would have been motivated to combine these teachings because signals involved in Th cell differentiation was a problem important in the art as evidenced by the teachings of Kuchroo *et al.* and Janeway *et al.*, for example. Based on the teachings of Linsley *et al.* and Kuchroo *et al.*, for example, one of ordinary skill in the art would have a reasonable expectation of success in modulating the immune response by immobilized, soluble, stimulatory B7-2. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Rabin, Ph.D. whose telephone number is (703) 305-6811. The examiner can normally be reached on Monday through Friday from 9:30 AM to 6:00 PM.

9. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The FAX number for this Group is (703) 305-7939. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Evelyn Rabin

Evelyn Rabin, Ph.D.

June 5, 1997

F. C. Eisenschenk

FRANK C. EISENSCHENK
PRIMARY EXAMINER
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6/6/97